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Studies in the Stereochemistry of Quinquevalent Nitrogen. IV.

By

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(Received February 2, 1916.)

I.

The Absorption Spectra of Quaternary Ammonium Compounds.

In an organic compound, isomers, caused by a difference of the configuration of atoms or atomic groups in the molecule, give similar ultra-violet absorption spectra; while those caused by a difference in the structure in the molecules, such as keto and enol forms, give dissimilar spectra.[1]

The author, in his II. article,[2] has shown that in the optically active methyl allyl phenyl benzyl ammonium compounds there exist optical isomers in α and γ forms which were assumed to be stereoisomers arising from the different configurations of the atomic groups in their molecules. This hypothesis was partly supported by the experiments[3] of autoracemisation conducted on these two isomers; but further confirmation was wanted.

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1 B. Hartley, J. Chem. Soc., **47**, 685 (1885); **77**, 840 (1900); Baly and Desch, *Ibid.*, **85**, 1029 (1904); Baly and Collie, *Ibid.*, **87**, 1343 (1905); Baly and Ewbank, *Ibid.*, **87**, 1355 (1905); Baly, Tuck and Marsden, *Ibid.*, **97**, 571 (1910); Purvis, *Ibid.*, **97**, 1553 (1910); Stewart, *Ibid.*, **91**, 1537 (1907); Hantzsch, Ber. D. Chem. Ges., **43**, 1651 (1910); Ley and Ulrich, *Ibid.*, **42**, 3441 (1909).

2 Mem. Coll. Sci., Kyoto, **1**, 123 (1915).

3 *Ibid.*, **1**, 231 (1915).

Recently interesting observations with regard to the nature of the valency of cobalt atom were made by Rutter and Nikolopulos[1] and also by Dr. Shibata[2] from a study of the absorption spectra of a cobalt complex.

Then, it was thought that a study of the ultra-violet absorption spectra of a quaternary ammonium compound might throw some light upon the combining way of atomic groups of pentavalent nitrogen atom and also upon the nature of the five valencies; and the present investigation was undertaken.

In the experiments, the absorption spectra of the compound were photographed with a quartz spectrograph from Adam Hilger, of N/100 and N/1000 solutions, changing the thicknesses of each solution from 100 to 1 mm. The source of the ultra-violet rays was obtained with an arc from iron electrodes.

The absorption curve was plotted from the photograph as usual, according to Hartley-Baly's method.[3]

EXPERIMENTAL PART.

1. *Hydrochlorides of ψ Cumidine and Benzyl Amine.*

According to Hartley[4] and Baly,[5] the author studied the ultra-violet absorption spectra of hydrochlorides of ψ cumidine and benzyl amine from Kahlbaum in the presence of hydrochloric acid to prevent the hydrolysis of the salts in their dilute aqueous solutions.

Under this condition, N/100 and N/1000 solutions of the salts gave the continuous absorption curves, as seen in Fig. I.

The salts persist in two absorption bands; and the heads of the bands were in ψ cumidine at about $1/\lambda$ 3500 and $1/\lambda$ 3700 and in benzyl amine $1/\lambda$ 3500 and $1/\lambda$ 4000 respectively.

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[1] Z. Phys. Chem., **82**, 361 (1913).

[2] J. Coll. Sci., Tokyo. **37**, 1 (1915); G. Urbain and Y. Shibata, Compt. rend., **157**, 593 (1913).

[3] J. Chem. Soc., **85**, 1029 (1904).

[4] *Loc. cit.*

[5] *Loc. cit.*

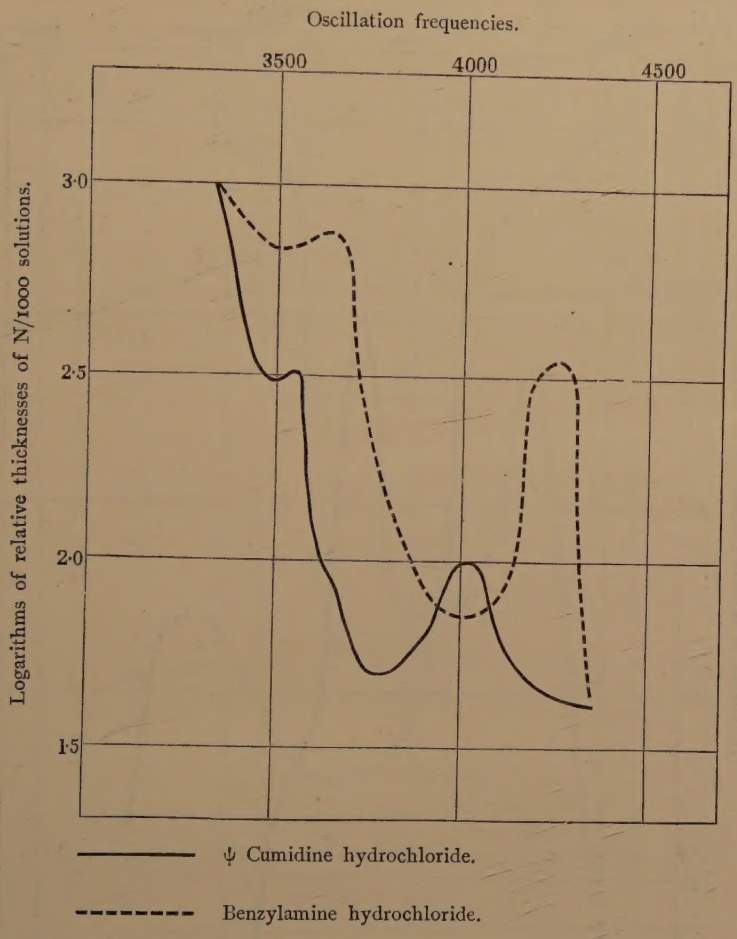


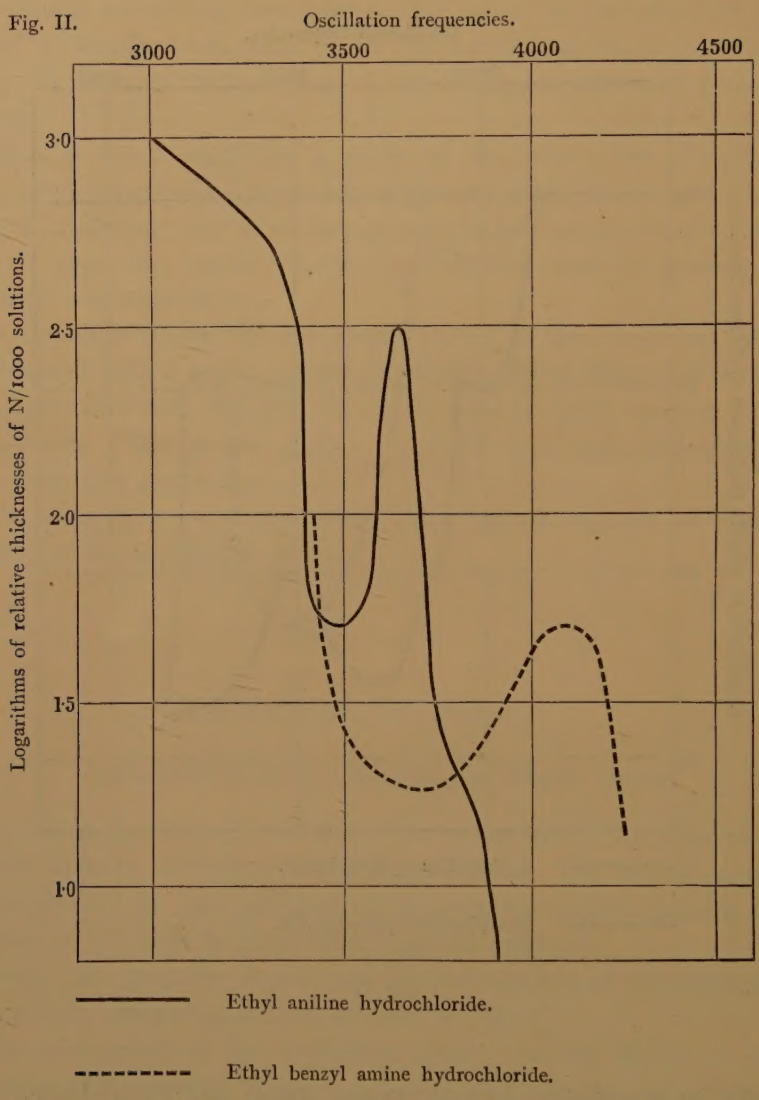
Fig. I.

2. Hydrochlorides of Ethyl Benzyl Amine and Ethyl Aniline.

The absorption spectra of the ultra-violet regions of N/100 and N/1000 solutions of these salts in the presence of an excess of hydrochloric acid have been studied, and the results are shown in Fig. II.

It will be noticed that there is only one absorption band in these secondary amine hydrochlorides and also that its position is more towards the red end of the spectrum than is that of the primary amine salt, the head of the band being about $1/\lambda$ 3500 — $1/\lambda$ 3600.

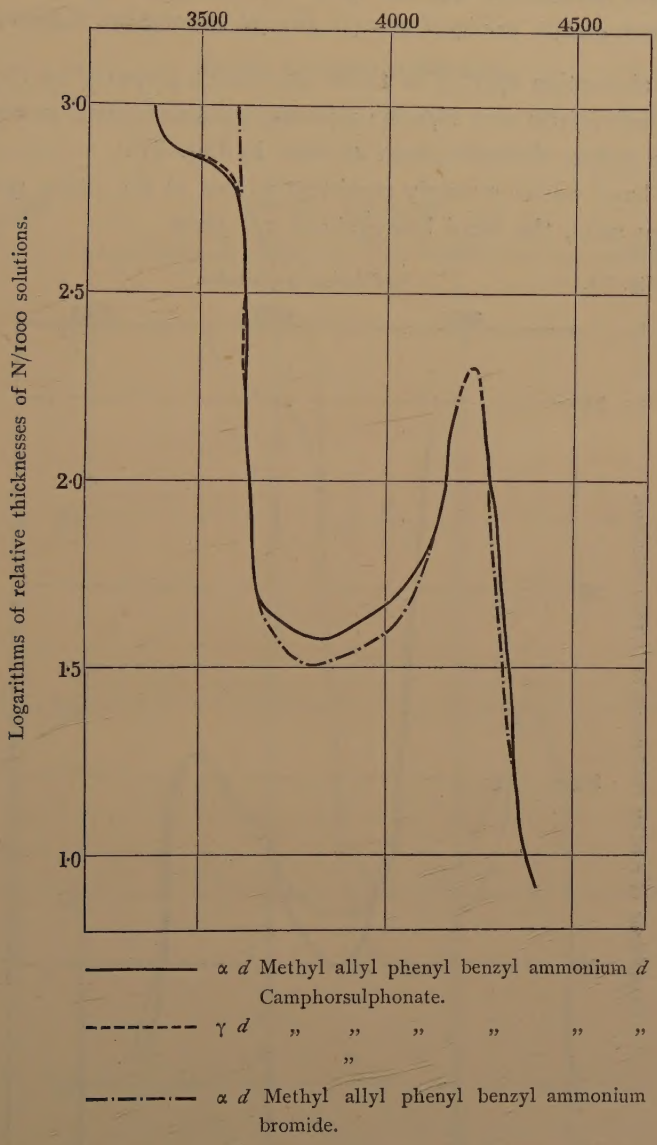
Fig. II.



3. α Dextro Methyl Allyl Phenyl Benzyl Ammonium Dextro Camphorsulphonate, α Dextro Methyl Allyl Phenyl Benzyl Ammonium Bromide and γ Dextro Methyl Allyl Phenyl Benzyl Ammonium Dextro Camphorsulphonate.

N/100 and N/1000 aqueous solutions of these substances, prepared by the author, were studied and the photographs are shown in Plates I, II & III; from which their absorption curves have been drawn as shown in Fig. III.

Fig. III. Oscillation frequencies.



The general form of the curves is similar and is very characteristic of ammonium salt as observed by Ley.[1] The band was strongly persistent, its head being about $1/\lambda$ 3800.

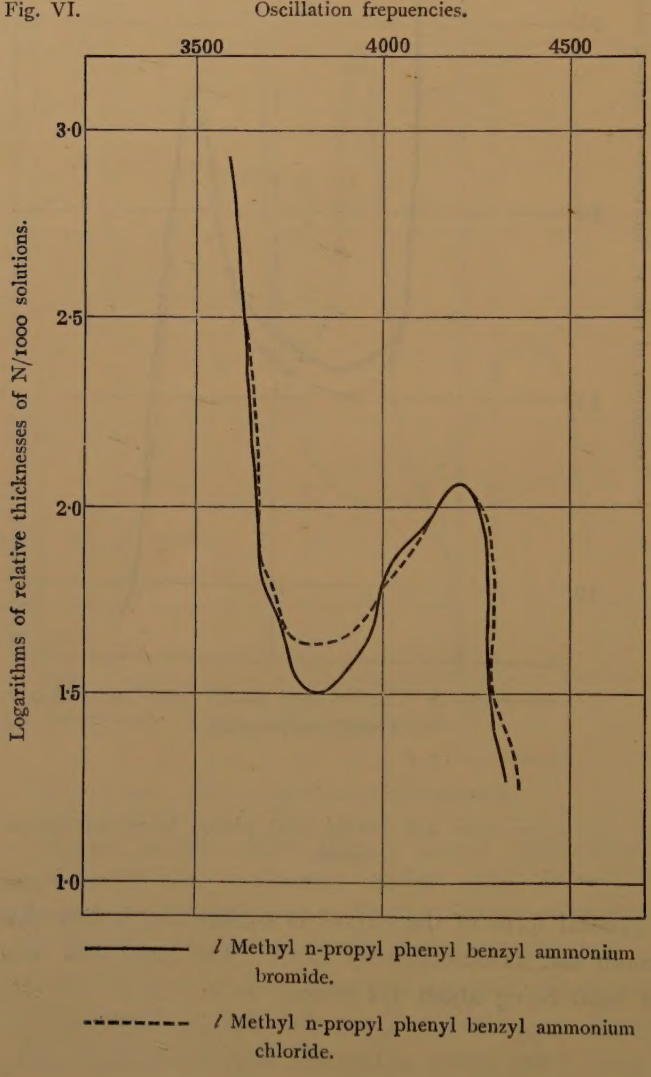
[1] *Loc. cit.*

4. Laevo Methyl n-Propyl Phenyl Benzyl Ammonium Bromide and Laevo Methyl n-Propyl Phenyl Benzyl Ammonium Chloride.

The absorption spectra of these substances, prepared by the author, were studied N/100 and N/1000 aqueous solutions gave a continuous absorption curve of similar form as seen in Fig. IV.

The band was as strongly persistent as that of the other quaternary ammonium salts, the head being about $1/\lambda$ 3800.

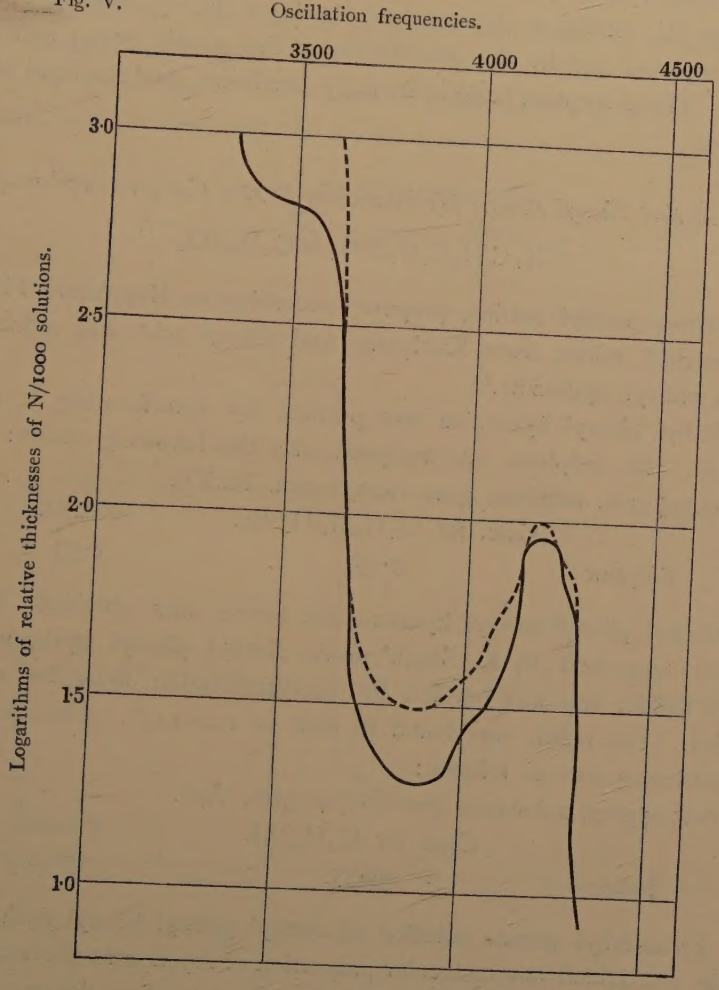
Fig. VI.



5. *Methyl Phenyl Benzyl Ethyl Acetate Ammonium Bromide and Methyl Phenyl Benzyl Ethyl Acetate Ammonium Dextro Camphorsulphonate.*

To see what change might take place in the absorption spectra by the substitution of the $CH_2COOC_2H_5$ group for the allyl group in the

Fig. V.



——— Methyl phenyl benzyl ethyl acetate ammonium *d* camphorsulphonate.

- - - - - - - - - Methyl phenyl benzyl ethyl acetate ammonium bromide.

quaternary ammonium compound above mentioned, the author prepared these substances and studied their absorption spectra in N/100 and N/1000 aqueous solutions.

The photograph of the absorption spectra of the camphorsulphonate is shown in plate IV.; and then plotted curve in Fig. V.

The absorption spectra of the ulter-violet rays as seen in Fig. V and plate IV, exhibit a characteristic band for the quaternary ammonium compound and by the substitution of the atomic group suffer no change. The absorption band is strongly persistent, and its head about $1/\lambda$ 3900.

6. Methyl Phenyl Benzyl Hydrazonium Dextro Camphorsulphonate,

$$CH_3.C_6H_5.C_7H_7.NH_2.N.C_{10}H_{15}SO_4.$$

Nitroso methyl aniline, prepared according to Hepp[1] and Fischer[2] from methyl aniline from Kahlbaum and nitrous acid, was reduced to methyl phenyl hydrazine.[3]

Methyl phenyl hydrazine was purified by transforming it to its sulphate. The sulphate was analysed with the following result:

0·3335 grm. sulphate gave 0·2092 grm. $BaSO_4$.

	Calc. for $C_{17}H_{10}N_2.H_2SO_4$.	Found.
Sulphur	9·19	8·53

Methyl phenyl benzyl hydrazonium iodide was obtained, by the method suggested B. K. Singh[4] from methyl phenyl hydrazine and benzyl iodide, and was purified by recrystallization from its aqueous solution. The iodide was found to melt at 122–123°. The analysis of the substance was as follows:

0·2504 grm. substance give 0·1740 grm. AgI.

	Calc. for $C_{14}H_{17}N_2I$.	Found.
Iodine	37·35	37·56

To an ethyl acetate solution of methyl phenyl benzyl hydrazonium iodide was added one molecular proportion of dry dextro silver camphorsulphonate; and the methyl phenyl benzyl hydragonium dextro camphor-

[1] Ber. D. Chem. Ges., **10**, 329 (1877).
[2] Lieb. Ann., **190**, 151 (1878).
[3] Fischer, *Ibid.*, **190**, 152 (1878).
[4] J. Chem. Soc., **105**, 1972 (1914).

sulphonate thus formed was purified by recrystallization from ethyl acetate solution. The camphorsulphonate crystallizes in white needles from ethyl acetate solution, and melts at 168–169°.

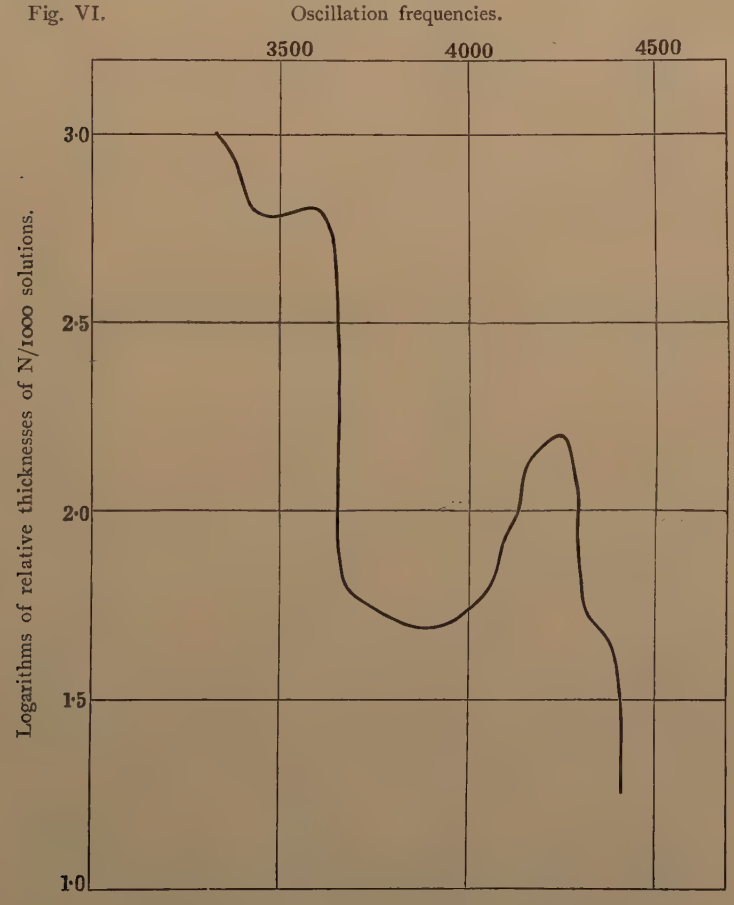
0·2165 grm. substance give 0·1095 grm. $BaSO_4$.

	Calc. for $C_{21}H_{32}O_4N_2S$.	Found.
Sulphur	7·21	6·95

The salt as seen from its properties and analysis, is identical with that obtained by Singh.[1]

On N/100 and N/1000 aqueous solutions of the salt the absorption spectra were studied and the result is shown in Fig. VI and Plate V.

Fig. VI.



Methyl phenyl benzyl hydrazonium *d* camphorsulphonate.

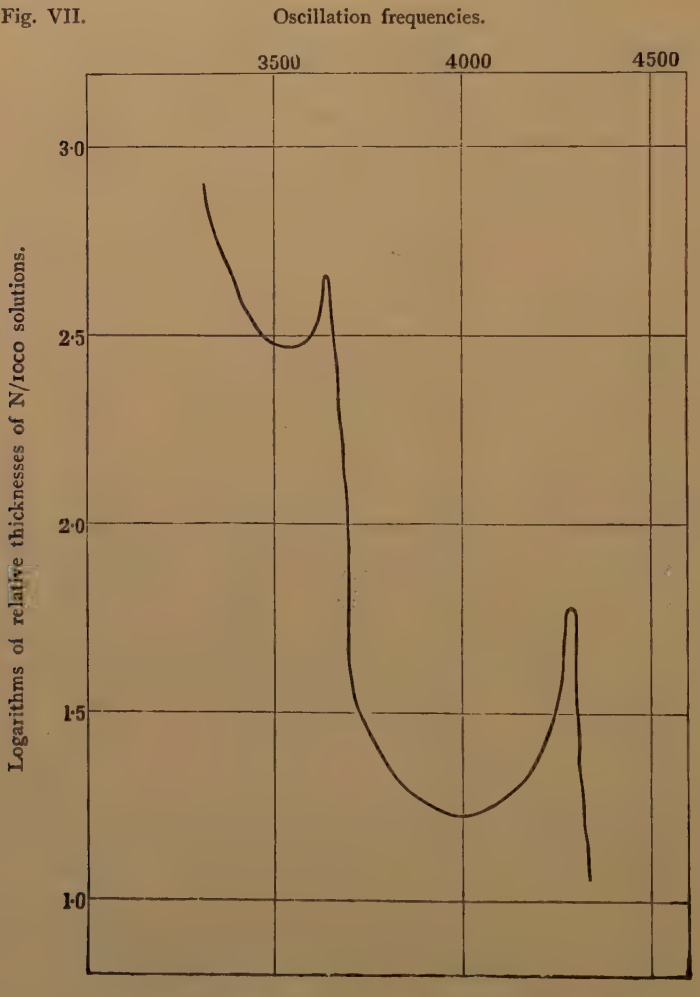
[1] *Loc. cit.*

The general form of the absorption curve is like that of the other quarternary ammonium salts, but the substitution of the NH_2 group for the alkyl group caused a little shift of the absorption band towards the violet end of the spectrum.

7. *Methyl Ethyl Phenyl Hydroxy Ammonium Chloride.*

N/100 and N/1000 aqueous solutions of the substance, prepared by the author (see experimental part of section II.), exhibit two ab-

Fig. VII.



Methyl ethyl phenyl hydroxy ammonium chloride.

sorption bands as seen in Fig. VII. and Plate VI. The heads of the bands are about $1/\lambda$ 3500 and $1/\lambda$ 4000. The alteration in the position of the bands and in the form of the curve must be due chiefly to the substitution of OH group for an alkyl group in the ammonium compound.

SUMMARY.

1. The absorption spectra of the ultra-violet rays of the quaternary ammonium compounds derived from aniline are independent of the atom or atomic group (with exception of iodine) combined with negative valency to the nitrogen atom.

2. The substitution of an alkyl group such as ethyl, propyl, allyl or benzyl or of $CH_2COOC_2H_5$ group for one of the methyl groups in trimethyl phenyl ammonium compounds, causes no apparent change in the absorption curve; while the introduction of an hydrogen atom, OH group or NH_2 group causes an alteration in its form and position.

3. The absorption spectra of ammonium compounds depend upon the nature of the atomic group combined with positive valency to the nitrogen.

4. In a quinquevalent nitrogen atom four "negative" valencies have a nature different from that of the fifth valency by which a negative atom or atomic group is combined to the nitrogen.

5. The isomers in methyl allyl phenyl benzyl ammonium compound should be stereoisomers but not structure isomers.

II.

Non-equivalence of the Five Valencies of Pentvalent Nitrogen.

In the previous section the author proved that the fifth "positive" valency of the nitrogen atom is different from the four "negative" valencies in a study of the absorption spectra of the ammonium compound.

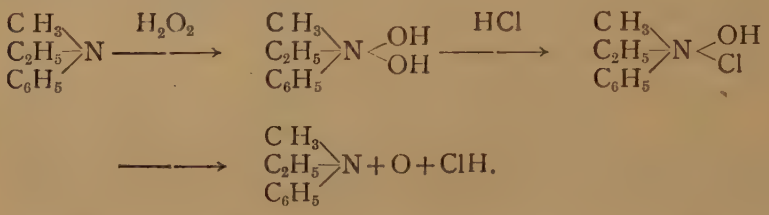
In order to get further confirmation of this conclusion from chemical reactions, the following experiments were carried out.

Some years ago Meisenheimer[1] prepared pairs of isomerides of the types $(CH_3)_3N<^{OR}_{OH}$ and $(CH_3)_3N<^{OH}_{OR}$ from trimethyl amine oxide, and

1 Ber. D. Chem. Ges., **33**, 1617 (1900).

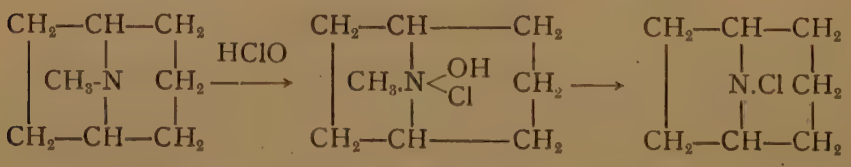
from a study of the decomposition products of these compounds presented important evidence upon the subject.

The author prepared methyl ethyl phenyl amine oxide according to Meisenheimer[1] from methyl ethyl aniline and hydrogen peroxide, and converted into methyl ethyl phenyl hydroxy ammonium chloride. The latter substance was subjected to distillation and was found to decompose into methyl ethyl aniline and hydrogen chloride. The mechanism of the reactions was assumed to be :



Furthermore, by the action of hypochlorous acid on methyl ethyl aniline, the author obtained a secondary amine as one of the reaction products, which assumed to be ethyl trichloro aniline.[2]

Willstätter and Iglauer[3] have shown that chloronortropidine was formed on adding tropidine to an aqueous solution of hypochlorous acid, and the following words are found in their article „ Die Einwirkung der unterchlorige Säure haben wir zu untersuchen begonnen bei tertiären, aliphatischen Basen, bei cyclischen Basen (N-Methylpiperidin, Tropan, Tropidin) und bei aromatischen Aminen ; das Dimethyl anilin liefert ein stechend riechendes, unbeständiges Oel, wahrscheinlich Methylphenyl-chlorostickstoff, welcher sich rasch durch Wanderung der Halogens in den Kern umwandelt,.....".



Breg[4] had already noticed that dialkyl chloroimide yields dialkyl amine upon the passing of dry hydrochloric acid upon its solution.

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1 Ber. D. Chem. Ges., **41**, 3966 (1908).

2 Chem. Zentralbl., **78**, I, 682 (1907).

3 Ber. D. Chem. Ges., **33**, 1638 (1900).

4 A. ch., [7] 3289 (1894).

$$\begin{matrix}R\\R\end{matrix}\!>\!N.Cl + HCl = \begin{matrix}R\\R\end{matrix}\!>\!N.H + Cl_2.$$

Infering from these facts, the author is led to believe that, in the present case methyl ethyl phenyl chloro ammonium hydroxide, a stereoisomer of methyl ethyl phenyl hydroxy ammonium chloride is first formed, which yields ethyl phenyl chloroamine with the elimination of methyl alcohol. The amine transformed by the rearrangement of chlorine atom from nitrogen to a carbon atom of benzene nuclear into ethyl chloroaniline, finally reacting with an excess of hypochlorous acid, yields ethyl trichloroaniline; thus the course of the reactions should be represented by the following scheme:

$$\begin{matrix}CH_3\\C_2H_5\\C_6H_5\end{matrix}\!>\!N \xrightarrow{HClO} \begin{matrix}CH_3\\C_2H_5\\C_6H_5\end{matrix}\!>\!N\!<\!\begin{matrix}Cl\\OH\end{matrix} \longrightarrow \begin{matrix}C_2H_5\\C_6H_5\end{matrix}\!>\!N.Cl$$

$$\longrightarrow \begin{matrix}C_2H_5\\Cl.C_6H_4\end{matrix}\!>\!N.H \xrightarrow{HClO} \begin{matrix}C_2H_5\\Cl_3C_6H_2\end{matrix}\!>\!NH.$$

EXPERIMENTAL PART.

1. *Decomposition of Methyl Ethyl Phenyl Hydroxy Ammonium Chloride.*

Methyl ethyl phenyl amine oxide, prepared by the oxidation of methyl ethyl aniline from Kahlbaum with 3% hydrogen peroxide, was purified by transforming into its picrate. The picrate was found to melt at 143–144°, though Meisenheimer gave 147–148° for its melting point. The result of the analysis was as follows:

0·1276 grm. picrate gave 0·2228 grm. CO_2 and 0·0577 grm. H_2O.

	Calc. for $C_{15}H_{16}O_8N_4$.	Found.
Carbon	47·37	47·62
Hydrogen	4·21	5·01

The picrate treated with conc. hydrochloric acid and pure methyl ethyl phenyl hydroxy ammonium chloride was obtained by crystallization from a chloroform-benzene solution.

The substance was analysed, and its chlorine content was determined.

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[1] *Loc. cit.*

0·138 grm. substance gave 0·1066 grm. AgCl.

	Calc. for $C_9H_{14}ONCl$.	Found.
Chlorine	18·94	19·12

When an aqueous solution of methyl ethyl phenyl hydroxy ammonium chloride was subjected to distillation, methyl ethyl aniline was abtained, as ascertained by analysis, and the melting point determination of the picrate.

0·1268 grm. amine picrate gave 0·2273 grm. CO_2 and 0·0604 grm. H_2O.

	Calc. for $C_{15}H_{15}O_7N_4$.	Found.
Carbon	49·59	49·12
Hydrogen	4·13	5·29

The same amine was also obtained by the decomposition of methyl ethyl phenyl amine oxide.

2. *Ethyl Trichloroaniline*, $C_2H_5.Cl_3C_6H_2NH$.

To an aqueous solution of methyl ethyl aniline hydrochloride an excess of hypochlorous acid, prepared by the method of Erlenmyer and Lipp,[1] was added with constant stirring. When the reaction was ended, the oily product, deposited on the bottom of the vessel, was separated from the mother liquor by decantation. The substance was treated with constic soda and water successively and extracted with ether. The etherial solution, dried with anhydrous sodium sulphate, was distilled to remove the solvent; and the residue was subjected to fractional distillation in vacuum. The fraction which boils between 127–130° at 15 mm is an yellow oil with an unpleasant odour.

I. 0·2482 grm. substance gave 0·4 grm. CO_2 and 0·1091 grm. H_2O.

II. 0·2026 grm. substance gave 0·3201 grm. CO_2 and 0·0811 grm. H_2O.

III. 0·3389 grm. substance gave 0·5842 grm. AgCl.

	Calc. for $C_8H_8NCl_3$.	Found.		
		I	II	III
Carbon	42·76	43·95	43·09	—
Hydrogen	3·56	4·88	4·44	—
Chlorine	47·44	—	—	42·67

[1] Leib. Ann., **219**, 185 (1883).

The substance, which is neither primary amine nor tertiary amine, yields a platinum double salt which melts at 180–181°.

The analytical result of the platinum double salt was as follows:

0·1013 grm. platinum double salt gave 0·0239 grm. Pt on ignition.

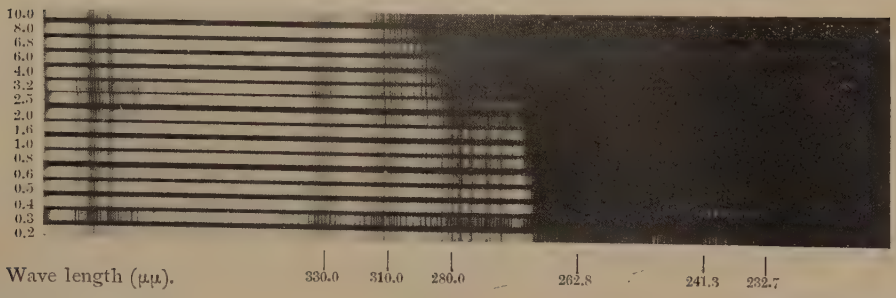
	Calc. for $C_{16}H_{18}N_2Cl_{12}Pt$.	Found.
Platinum	22·70	23·57

In conclusion, the author wishes to express his thanks to Asst.-Prof. Yuji Shibata, of Tokyo Imperial University, for his kind help in preparing the absorption spectra in this work.

Pt. I.

Thickness (cm.)

α d Methyl allyl phenyl benzyl amm. d camphorsulphonate, $\frac{1}{100}$ N.

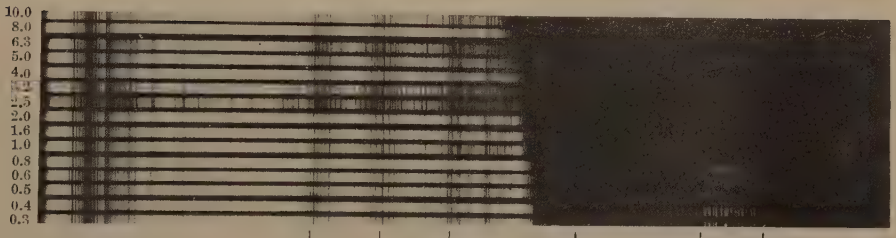


Wave length (μμ). 330.0 310.0 280.0 262.8 241.3 232.7

Pt. II.

Thickness (cm.)

α d Methyl allyl phenyl benzyl amm. bromide, $\frac{1}{100}$ N.

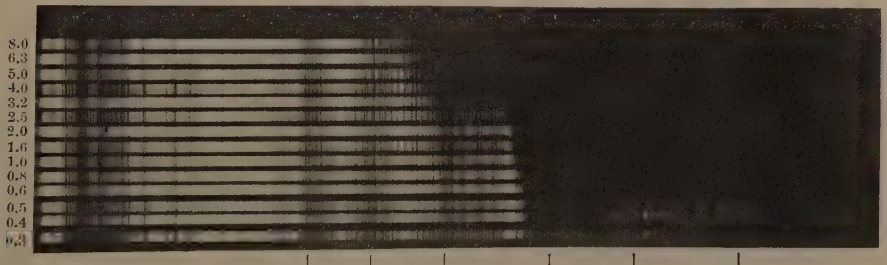


Wave length (μμ). 330.0 310.0 280.0 262.8 241.3 232.7

Pt. III.

Thickness (cm.)

γ d Methyl allyl phenyl benzyl amm. d camphorsulphonate, $\frac{N}{100}$

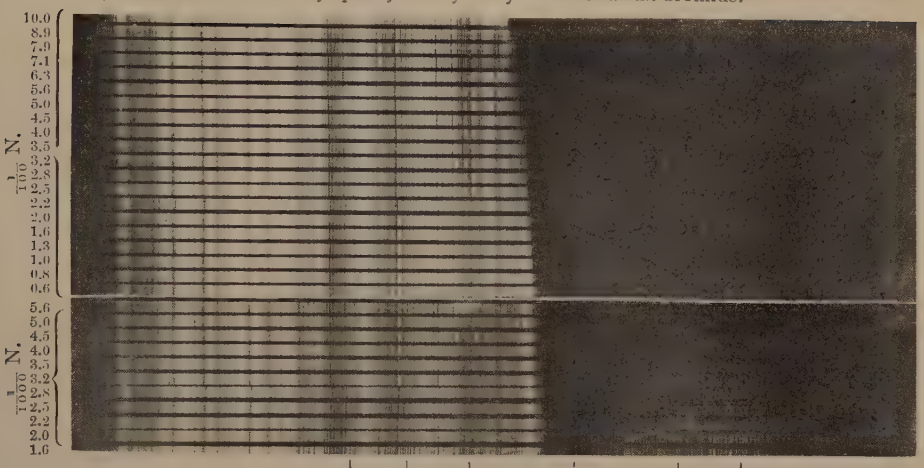


Wave length (μμ). 330.0 310.0 280.0 262.8 241.3 232.7

Pt. IV.

Thickness (cm.)

Methyl phenyl benzyl ethyl acetates amm. bromide.

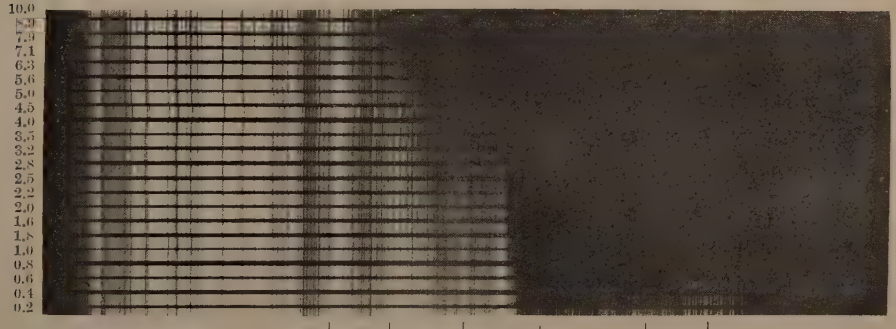


Wave length (μμ). 330.0 310.0 280.0 262.8 241.3 232.7

Pt. V.

Thickness (cm.)

Methyl phenyl benzyl hydrazonium d. camphorsulphate, $\frac{N}{100}$.

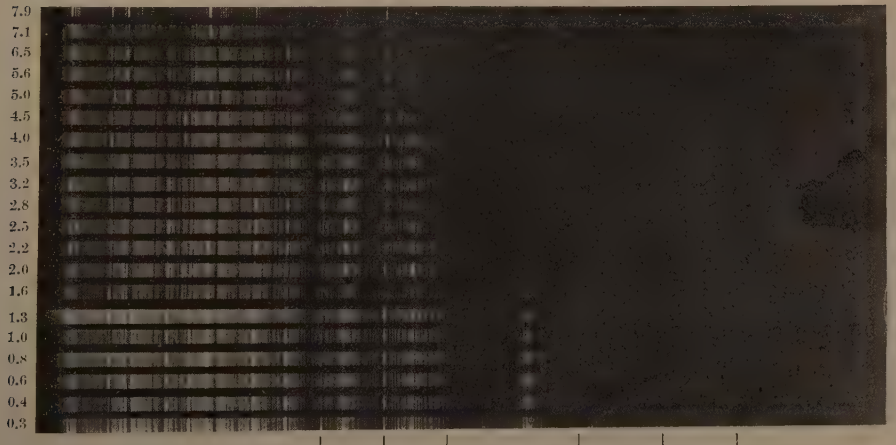


Wave length (μμ). 330.0 310.0 280.0 260.8 241.3 232.7

Pt. VI.

Thickness (cm.)

Methyl ethyl phenyl hydroxy amm. chloride, $\frac{1}{100}$ N.



Wave length (μμ). 330.0 310.0 280.0 262.8 241.3 232.7

The Influence of the Acid Radicals containing the Different Secondary Alkyls upon the Narcotic Action of Urethane.

By

Isao Odaira.

(Received February 3, 1916.)

It is already known that the narcotic action of urethane is due to the ethyl radical present in the form of an ester of carbamic acid and at the same time such a radical would effect the lowering of the blood-pressure, while the amino group would exert an action upon the circulatory system and the respiratory centre, in such a way as to cause the elevation of the blood-pressure and the stimulation of the latter. Now owing to such characteristic physiological actions which may be caused by the ethyl radical on one hand and by the amino group on the other, it may be assumed that urethane is comparatively free from its disgusting by-effects.[1] Binet[2] states that the strengths of the narcotic action and poisonous effects of the homologues of urethane are dependent upon the number of carbon atoms present in the alkyl radicals, that is, more the carbon atoms present in the alkyl radicals are exhibited more the narcotic action and poisonous by-effects; the latter, however, disappear or at least decrease by the acetylation of the amino group while the narcotic action remains unchanged. Based upon the experiment with animals he has shown the relative strengths of their poisonous effects by the following scale:

$NH_2.CO.OCH_3$.....2·0	$NH_2.CO.OC_2H_5$.....4·0
$CH_3.CO.NH.CO.OCH_3$.....1·0	$CH_3.CO.NH.CO.OC_2H_5$.....1·5

1 Fränkel, Arzneimittel Synthese, 3rd ed. pp. 488, 505; Morishuna, Arzneimittel-Lehre 4th ed. p. 271.

2 Rev. med. Suisse Rom., 1893, 540, 628. Fränkel, Arzneimittel-Synthese, 3rd ed. p. 488.

At the suggestion of Prof. Kuhara the auther has undertaken the study of the influence of the different acid radicals containing the secondary alkyls such as R_2CH- or $RR'CH-$ upon the narcotic action of urthane, expecting that the increase of the number of carbon atoms in R and R′ may make its narcotic action more and more effective to some extent, as are seen in the substances of the veronal and sulfonal groups, simultaneously with the decrease of its poisonous effects.

From such a point of view the auther has synthesized the different acyl derivatives of urethane of the following formulas by the action of the acyl chlorides containing the different secondary alkyls upon urethane:

$$\begin{matrix} R \\ R \end{matrix}\!>\!CH.CO.NH.CO.OC_2H_5 \text{ and } \begin{matrix} R' \\ R \end{matrix}\!>\!CH.CO.NH.CO.OC_2H_5$$

and represents them by the special names, as will be seen in the following list:

1. Diethylaceturethane, Detonal,

$$\begin{matrix} C_2H_5 \\ C_2H_5 \end{matrix}\!>\!CH.CO.NH.CO.OC_2H_5.$$

2. Ethylpropylaceturethane, Epronal,

$$\begin{matrix} C_2H_5 \\ C_3H_7 \end{matrix}\!>\!CH.CO.NH.CO.OC_2H_5.$$

3. Dipropylaceturethane, Dipronal,

$$\begin{matrix} C_3H_7 \\ C_3H_7 \end{matrix}\!>\!CH.CO.NH.CO.OC_2H_5.$$

4. Propylbutylaceturethane, Probnal,

$$\begin{matrix} C_3H_7 \\ C_4H_9 \end{matrix}\!>\!CH.CO.NH.CO.OC_2H_5.$$

5. Dibutylaceturethane, Dibnal,

$$\begin{matrix} C_4H_9 \\ C_4H_9 \end{matrix}\!>\!CH.CO.NH.CO.OC_2H_5.$$

Further, the following substances have also been synthesized by the author for comparison with the above-mentioned narcotics:

6. Oenanthylylurethane,

$$CH_3(CH_2)_5CO.NH.CO.OC_2H_5.$$

7. N-Isoamylurethane,

$$\begin{matrix} C_2H_5 \\ C_2H_5 \end{matrix}\!\!>\!CH.NH.CO.OC_2H_5.$$

8. *α*-Bromethylpropylaceturethane,

$$\begin{matrix} C_2H_5 \\ C_2H_5 \end{matrix}\!\!>\!CBr.CO.NH.CO.OC_2H_5.$$

Of those compounds the auther has paid an attention specially to detonal and epronal at first, with regard to their physiological actions by making experiments with frogs and rabbits in which foremostly their narcotic actions in comparison with those of known narcotics and then their influences upon the heart, blood-vessels, respiratory centre and vagus were examined, since it is almost common that the impediments in the heart and lungs follow as the by-effects of narcotics.

As will be seen in the results of experiments executed with Rana esculenta and shown in Table V. given in the experimental part detonal seems to stand in parallel with amylene and chloral hydrates, yet to be more effective than urethane in the narcotic action, whose strength is represented in this case by the duration of sleep; epronal is still more effective being almost equal to veronal and hedonal, nevertheless its action much more prompt than that of any other narcotic in comparison.

The experiments on the stoppage of the heart-beat which may be brought about by narcotics were performed by charging the solutions of the different narcotics dissolved in Ringer's solution to the extirpated hearts of Rana esculenta in the equal heights of column. The results show that detonal is least poisonous, and epronal almost equal to bromural but somewhat less poisonous than hedonal.

Moreover, the auther has conducted the experiments for the determination of the minimum and lethal doses of epronal for the rabbit. By giving 0·3 grm. of epronal to the rabbit per 1 kilog. by its weight the sedative condition followed as an effect, and by 0.5 grm. the sleep continued for an hour. By increasing doses, however, successively to 1·0, 1·5 and 2·0 grm, the rabbits fell into a deep sleep, and by 2·5 and 3·0 grm. died after 20–50 hours.

By dosing 1·5 grm. epronal per 1 kilog. rabbit the blood-pressure was observed to be 100 mm. in the mercury column, as is usually noticed in the normal rabbits, and the vagus and respiratory centre

were not influenced at all, as will be seen in the curve given in the experimental part.

According to H. H. Meyer[1] the coefficient of distribution between oil and water of the narcotic of the aliphatic series is the factor of narcotic action. The author has attempted to examine such a view with regard to detonal and epronal in comparison with some of already known narcotics by determining their coefficients of distribution, according to the method described in the experimental part, the intervals between injection and sleep and the durations of sleep. In the experiments 0·2 cc. of 0·15% solution of each narcotic per 1 grm. frog were injected, and the quantity of each was returned in term of gram-mol. per 1 grm. frog, the results of experiments being given in the following table:

TABLE I.

Narcotics.	Coefficients of distribution, (K).	Gram-mol. per 1 grm. frog.	Intervals between injection and sleep.		Durations of sleep.	
			Hr.	Min.	Hr.	Min.
Trional	4·60	124×10^{-8}	0	14	1	40
Epronal	3·30	149×10^{-8}	0	5	1	51
Detonal	1·70	161×10^{-8}	Merely in sedative condition			
Bromural	1·33	137×10^{-8}	0	15	5	30
Chloralhydrate	0·22	181×10^{-8}	Merely in sedative condition			
Urethane	0·13	337×10^{-8}	„	„	„	„
Veronal	0·119	166×10^{-8}	0	32	2	0

As seen from Table I. the coefficients of distribution do not stand in harmony with the durations of sleep, but seem to have some relation with the intervals between injection and sleep, except the case of trional, that is, higher the coefficient of distribution of narcotic more prompt its action may be.

On continuing the pharmacological study of dipronal, probnal, dibnal, oenanthylylurethane, N-isoamylurethane and α-bromethylpropylaceturea in comparison with urethane, detonal and epronal, the following results were obtained:

[1] Fränkel, Arzneimittel Synthese, 3rd ed. p. 511.

TABLE II.

Narcotics.	Chem. formulas.	Minimum doses per 1 grm. frog in aq. solution, in gram-mol.	Minimnm doses per 1 grm. frog in emulsion, in gram-mol.	Strengths of narcotic action.	Ratios of strengths.	Solubilities in 100 parts water at 20°.
Urethane	$NH_2.CO.OC_2H_5$	1910×10^{-8}	—	10	—	—
Detonal	$(C_2H_5)_2CH.CO.NH.CO.OC_2H_5$	214×10^{-8}	5560×10^{-9}	90	9·0	0·550
Epronal	$C_2H_5(C_3H_7)CH.CO.NH.CO.OC_2H_5$	112×10^{-8}	1990×10^{-9}	170	1·9	0·150
Dipronal	$(C_3H_7)_2CH.CO.NH.CO.OC_2H_5$	56×10^{-8}	—	340	2·0	0·040
Probnal	$C_3H_7(C_4H_9)CH.CO.NH.CO.OC_2H_5$	39×10^{-8}	655×10^{-9}	500	1·5	0·032
Dibnal	$(C_4H_9)_2CH.CO.NH.CO.OC_2H_5$	—	658×10^{-9}	500	1·0	0·008
Oenanthylyl-urethane	$CH_3(CH_2)_5CO.NH.CO.OC_2H_5$	—	2985×10^{-9}	90-170	—	0·021
N-Isoamyl-urethane	$(C_2H_5)_2CH{-}{-}NH.CO.OC_2H_5$	200×10^{-8}	—	95	—	0·409
Adaline	$(C_2H_5)_2CBr.CO.NH.CO.NH_2$	34×10^{-8}	—	560	—	—
α-Bromethyl-propylaceturea	$C_2H_5(C_3H_7)CBr.CO.NH.CO.NH_2$	24×10^{-8}	—	800	1·4	0·041

The strengths of narcotic action in this case have been deduced from the minimum doses of the narcotics in aqueous solution and in emulsion, as will be explained in the experimental part.

Referring the table it is noticed that the increase in the number of carbon atoms of R and R′ in the acid radicals containing the secondary alkyls such as $(R_2CH)'$ or $(RR'CH)'$ would evidently exert an influence upon the narcotic action making it more and more effective, possibly reaching the maximum value at probnal or propylbutylacet-urethane, while in the higher homologues perhaps no more increase of action may take place as probnal and dibnal do not show difference in the strengths of action. Also it is seen that the same relation exists in the adaline series. The auther has synthesised α-bromethylpropyl-aceturea, which is analogous in structure with adaline but richer in carbon atoms than the latter, and then conducted their comparative experiments on the strengths of their narcotic action, in which we have observed

that just as in the case of urethane series *α*-bromethylpropylaceturea is much more effective than its lower homologue, adaline.

Oenanthylylurethane which contains the acid redical consisting of a primary alkyl and is isomeric with epronal, possesses a notably less narcotic action then the latter; hence the secondary alkyl must be more energetic in action than the primary.

In the case of N-isoamylurethane which differs in constitution from detonal by the lack of the carbonyl group, its narcotic action has been found to be somewhat stronger than that of detonal, but its poisonous character far more energetic than that of the latter, as noticed in the experiments on the failure of the heart. The presence of the carbonyl group, therefore, seems not to exert a remarkable influence upon the narcotic action, but evidently to decrease the poisonous character of the substance.

The solubilities of the urethane derivatives of the homologous series containing the acid radicals consisting of the secondary alkyl groups seem to have an intimate relation with the narcotic action, that is, the narcotic action may be inversely propartional to the solubility with the exception of dibnal. Moreovere, in such substances of the homologous series, their action upon the heart becomes more and more effective as their narcotic action increases.

EXPERIMENTAL PART.

I. Synthesis of the Different Acylurethanes and Some Allied Compounds.

1. *Diethylaceturethane* (*Detonal*),

$$\begin{matrix} C_2H_5 \\ C_2H_5 \end{matrix}\!\!>\!CH.CO.NH.CO.OC_2H_5.$$

For preparing this substance a mixture of diethylacetyl choride, $(C_2H_5)_2CH.COCl$,[1] from diethylacetic acid[2] and urethane was heated in a flask provided with an inverted condenser over a water bath for an hour. The product, when cooled, was treated with a dilute solution of sodium carbonate and filtered, and the residue was washed with cold water and then made to crystallize from alcohol. Detonal consists of colourless

[1] Ber. D. chem. Ges., **23**, 189.

[2] Lieb. Ann., **204**, 141.

needle-shaped crystals which fuse at 88°, and is somewhat volatile. It is soluble in 190 parts of water but easily in alcohol, ether, chloroform and benzene. It decomposes by heating with a solution of an alkali evolving ammonia, and then by treating the product with an acid an oil separates out with the evolution of carbon dioxide. The analysis of the substance gave the following results:

I 0·2331 grm. substance gave 0·4785 grm. CO_2 and 0·1885 grm. H_2O.
II 0·1534 „ „ „ 0·3999 „ „ „ 0·1245 „ „
III 0·2451 „ „ „ 16·1 cc. N at 13° and 771 mm.
VI 0·1483 „ „ „ 9·5 cc. „ 15° „ 774 mm.

	Calculated for $C_9H_{17}NO_3$.	Found.			
		I	II	III	IV
Carbon	57·75	57·15	57·73	—	—
Hydrogen	9·07	9·09	9·01	—	—
Nitrogen	7·49	—	—	7·92	7·66

With an expectation to convert detonal into more soluble form, the auther has attempted to prepare its sodium compound which is possible to be formed in its enol form, by treating detonal dissolved in alcohol with alcoholic sodium ethylate, but efforts ended in vain. From the product of reaction, however, there separated out after 24 hours colourless crystals which were repeatedly washed with alcohol and ether, and dried over sulphuric acid. The substance partly decomposes at 70°, and its aqueous solution evolves carbon dioxide by the addition of hydrochloric acid or simply by boiling, and gives the iodoform reaction. The substance must, therefore, be sodium ethylcarbonate, as is confirmed by the following analytical results:

I 0·1081 grm. substance gave 0·1287 grm. CO_2 and 0·0413 grm. H_2O.
II 0·3066 „ „ „ 0·1981 „ Na_2SO_4.

	Calculated for $C_3H_5O_3Na$.	Found.	
		I	II
Carbon	32·14	32·47	—
Hydrogen	4·46	4·28	—
Sodium	20·53	—	20·95

The mother liqueur from the crystals of sodium ethylcarbonate was evaparated to dryness, and the residue subjected to sublimation, by which process colourless needle-shaped crystals melting at 112° were

deposited. By heating the crystals with a solution of an alkali ammonia was found to be liberated and by acidifing the product of reaction we got an oily substance; hence the crystals ought to be diethylacetamide and the oil diethylacetic acid. The analysis of the crystals gave the following results:

I 0·1074 grm. substance gave 0·2457 grm. CO_2 and 0·1070 grm. H_2O.
II 0·1058 „ „ „ 0·2437 „ „ „ 0·1031 „ „
III 0·1045 „ „ „ 11 cc. N at 17° and 761·8 mm.

	Calculated for $C_6H_{13}NO$.	Found.		
		I	II	III
Carbon	62·62	62·38	62·81	—
Hydrogen	11·30	11·21	10·92	—
Nitrogen	12·17	—	—	12·33

The decomposition of detonal by sodium ethylate, therefore, would be represented as follows:

$$\begin{matrix} C_2H_5 \\ C_2H_5 \end{matrix}\!\!>\!CH.CO.NH.CO.OC_2H_5 + HONa \longrightarrow$$

$$\begin{matrix} C_2H_5 \\ C_2H_5 \end{matrix}\!\!>\!CH.CO.NH_2. + NaO.CO.OC_2H_5.$$

2. *Ethylpropylaceturethane* (*Epronal*),

$$\begin{matrix} C_2H_5 \\ C_3H_7 \end{matrix}\!\!>\!CH.CO.NH.CO.OC_2H_5.$$

Epronal was obtained from urethane and ethylpropylacetyl chloride from ethylpropylacetic acid prepared according to the statement by Schukowski.[1] The process was almost wholly analogous with the preparation of detonal. Epronal consists of colourless needle-shaped crystals which fuse at 72°. It is soluble in 700 parts of cold water, but readily in alcohol, ether, chloroform and benzene. Its chemical behaviours are similar to those of detonal. The analysis of the substance gave the following values for carbon, hydrogen and nitrogen:

I 0·1810 grm. substance gave 0·3944 grm. CO_2 and 0·1525 grm. H_2O.
II 0·1703 „ „ „ 0·3903 „ „ „ 0·1513 „ „

[1] Ber. D. chem. Ges., R. **21**, 57.

III 0·1712 „ „ „ 12·5 cc. N at 12° and 760·3 mm.
IV 0·1967 „ „ „ 12·7 cc. „ „ 13° „ 760·3 mm.

	Calculated for $C_{10}H_{19}NO_3$.	Found.			
		I	II	III	IV
Carbon	59·70	59·42	59·30	—	—
Hydrogen	9·45	9·51	9·96	—	—
Nitrogen	6·97	—	—	7·37	7·44

3. *Dipropylaceturethane*, (*Dipronal*),

$$\begin{matrix} C_3H_7 \\ C_3H_7 \end{matrix}\!\!>\!CH.CO.NH.CO.OC_2H_5.$$

This substance was prepared from urethane and dipropylacetyl chloride from dipropylacetic acid obtained by following Schukowski's[1] method. It crystallizes in colourless needles melting at 88–89°. It is soluble in 2500 parts of water at 20°, but readily in alcohol, ether, chloroform and benzene. Its chemical behaviours are similar to those of detonal and epronal. The analysis of the substance gave the following results:

I 0·1526 grm. substance gave 0·3441 grm. CO_2 and 0·1357 grm. H_2O.
II 0·1218 „ „ „ 6·6 cc. N at 12° and 764 mm.

	Calculated for $C_{11}H_{21}NO_3$.	Found.	
		I	II
Carbon	61·40	61·49	—
Hydrogen	9·77	9·97	—
Nitrogen	6·51	—	6·61

4. *Propylbutylaceturethane* (*Probnal*),

$$\begin{matrix} C_3H_7 \\ C_4H_9 \end{matrix}\!\!>\!CH.CO.NH.CO.OC_2H_5.$$

This substance was prepared from urethane and propylbutylacetyl chloride from propylbutylacetic acid obtained according to Schukowski's method.[2] It crystallizes in colourless needles melting at 69–70°. The

1 Ber, D. chem. Ges., R. **21**, 57.
2 *Ibid.*

substance dissolves in 3125 parts of water at 20°, while it is easily soluble in alcohol, ether, chloroform and benzene. Its chemical behaviours resemble those of dipronal. The analysis gave the following results:

I 0·1255 grm. substance gave 0·2866 grm. CO_2 and 0·1142 grm. H_2O.
II 0·1316 „ „ „ 6·9 cc. N at 11° and 763 mm.

	Calculated for $C_{12}H_{23}NO_3$.	Found.	
		I	II
Carbon	62·88	62·29	—
Hydrogen	10·05	10·20	—
Nitrogen	6·11	—	6·28

5. *Dibutylaceturethane* (*Dibnal*),

$$\begin{matrix} C_4H_9 \\ C_4H_9 \end{matrix}\!\!>\!CH.CO.NH.CO.OC_2H_5.$$

This substance was obtained from urethane and dibutylacetyl chloride from dibutylacetic acid by the method analogous to those of the preceding acylurethanes. It crystallizes in colourless needles melting at 44°. The substance dissolves in 12500 parts of water, while it is readily soluble in alcohol, ether, chloroform and benzene. Its chemical characters are similar to those of probnal. The analytical results are as follows:

I 0·1232 grm. substance gave 0·2895 grm. C_2O and 0·1150 grm. H_2O.
II 0·1341 „ „ „ 6·6 cc. N at 13° and 764 mm.

	Calculated for $C_{13}H_{25}NO_3$.	Found.	
		I	II
Carbon	64·20	64·08	—
Hydrogen	10·29	10·46	—
Nitrogen	5·76	—	5·86

6. *Oenanthylylurethane*,

$$CH_3.(CH_2)_5.CO.NH.CO.OC_2H_5.$$

This substance was obtained from urethane and Oenanthylyl chloride from oenanthylic acid prepared by oxidizing castor oil with nitric acid. Oenanthylylurethane crystallizes in colourless thin plates melting at 67°,

and dissolves in 4762 parts of water. It is readily soluble in alcohol, ether, benzene and chloroform. The analysis of the substance gave the following results:

I 0·1217 grm. substance gave 0·2640 grm. CO_2 and 0·1038 grm. H_2O.
II 0·1348 „ „ „ 8·1 cc. N at 11° and 761 mm.

	Calculated for $C_{10}H_{19}NO_3$.	Found.	
		I	II
Carbon	59·70	59·16	—
Hydrogen	9·45	9·57	—
Nitrogen	6·97	—	7·18

7. *N-Isoamylurethane,*

$$\begin{matrix} C_2H_5 \\ C_2H_5 \end{matrix}\!\!>\!CH.NH.CO.OC_2H_5.$$

The substance was prepared according to the method given by Lengfeld and Stieglitz,[1] which is based upon the Beckmann rearrangement of acidbromamide by the action of sodium alcoholate. In this case diethylacetamide and sodium ethylate were used. It is a colourless fragrant oil boiling at 155° (460 mm.) and its 1 part dissolves in 244 parts of water at 20°. Its analysis gave the following values:

I 0·1230 grm. substance gave 0·2686 grm. CO_2 and 0·1200 grm. H_2O.
II 0·1414 „ „ „ 10·3 cc. N at 12° and 763 mm.

	Calculated for $C_8H_{17}NO_2$.	Found.	
		I	II
Carbon	60·38	59·55	—
Hydrogen	10·69	10·93	—
Nitrogen	8·81	—	9·05

8. *α-Bromethylpropylaceturea,*

$$\begin{matrix} C_2H_5 \\ C_3H_7 \end{matrix}\!\!>\!CBr.CO.NH.CO.NH_2.$$

This compound was prepared by the action of α-bromethylpropylacetylbromide upon urea. It crystallizes in colourless needles, which

[1] Amer. Chem. J. **15**, 504; **16**, 370.

fuse at 97° in the state of opacity but clearly at 105°. Its 1 part dissolves in 2439 parts of water at 20°. It is, however, readily soluble in alcohol, ether, benzene and chloroform. The analysis gave the following results:

I 0·1405 grm. substance gave 0·1969 grm. CO_2 and 0.0772 grm. H_2O.
II 0·0957 „ „ „ 9·5 cc. N at 10° and 763 mm.
III 0·1211 „ „ „ 0·0892 grm. AgBr.

	Calculated for $C_8H_{13}N_2O_2Br$.	Found.		
		I	II	III
Carbon	38·25	38·22	—	—
Hydrogen	5·98	6·16	—	—
Nitrogen	11·15	—	11·64	—
Bromine	31·87	—	—	31·35

II. The Coefficients of Distribution.

The determination of the coefficients of distribution between oil and water was performed at 17–20° using those two substances as solvents. Olive oil (Ph. J. III), as selected in this case, was rectified by shaking with a dilute solution of sodium carbonate, and then by separating an oily layer with sodium chloride which was washed with water until the alkaline reaction disappears.

A certain quantity of a narcotic was dissolved in olive oil so rectified, to which equal quantity of water was added, and the mixture shaked for 24 hours. Having allowed the latter to stand for 2 days, the aqueous layer was separated, and then saturated with hydrochloric acid by passing its current. The aqueous solution, so saturated, was heated in a sealed tube at 130° for 5 hours. Now the contents of the tube were evaparated in order to drive out a greater part of hydrochloric acid, then diluted with water and neutralized, again diluting to a certain definite volume. Having taken a definite quantity of such a solution, the quantity of ammonia was determined by mean of Nessler's solution with the aid of a colorimeter. From the amount of ammonia thus found the quantity of the narcotic dissolved in the aqueous part can be calculated. Denoting the quantity of the narcotic dissolved in water

by W and that of the same first taken by S we can get its coefficient of distribution by the formula,

$$K = \frac{S - W}{W}$$

In the case of the non-valatilie narcotic, however, we can directly determine the amount in an aqueous solution by evaporating to dryness. The results of experiments will be given in the following table:

TABLE III.

Narcotics.	Narcotics taken in gram.	Water taken in gram.	Olive oil taken in gram.	Narcotics in gram transferred to water.	K.
Epronal	0·10	30	30	0 0229	3·300
„	0·10	30	30	0·0228	3·400
Detonal	0·10	30	30	0·0361	1·800
„	0·70	80	80	0·2607	1·700
Urethane	1·00	30	30	0·8834	0·132
Veronal	0·10	50	50	0·0900	0·111
„	0·15	50	50	0·1340	0·119
Trional	0·15	40	40	0·0145	4·600

III. The Relative Strengths of the Narcotic Action.

The auther had to represent in the experiments (1) and (2) the strength of the narcotic action of a substance by the length of time in which the frog (Rana esculenta) can not release from the dorsal position with its own power.

The following tables show the mean values obtained for the different narcotics, arranged according to the concentration of solutions, having been deduced from the experimental results.

(1) The different narcotics each in 0·00025 grm. per 1 grm. frog were injected in the different concentrations:

TABLE IV.

Narcotics.	Concentration of solutions in %.	Intervals between injection and sleep.		Intervals between injection and the stoppage of respiration.		Durations of sleep.		Durations of the cessation of respiration.		Intervals between awaking and recovery.	
		Hr.	Min.	Hr.	Min.	Hr.	Min.	Hr.	Min.	Hr.	Min.
Veronal	0·50	0	20	0	20	4	19	4	19	3	30
Hedonal	0·80	0	9	0	19	3	33	3	19	2	0
Epronal	0·15	0	16	0	25	0	56	0	26	0	40
Detonal	0·50	Released from the dorsal position with difficulty									

(2) The different narcotics each in 0·0003 grm. per 1 grm. frog were injected in the same concentration:

TABLE V.

Narcotics.	Concentration of solutions in %.	Intervals between injection and sleep.		Intervals between injection and the stoppage of respiration.		Durations of sleep.		Durations of the cassation of respiration.		Intervals between awaking and recovery.	
		Hr.	Min.	Hr.	Min.	Hr.	Min.	Hr.	Min.	Hr.	Min.
Veronal	0·15	0	32	0	32	2	0	2	0	5	30
Hedonal	„	0	7	0	7	1	55	1	55	2	0
Epronal	„	0	5	0	5	1	51	1	51	2	30
Bromural	„	0	15	0	15	5	30	5	30	3	0
Trional	„	0	14	0	14	1	14	1	14	1	20
Chloralhydrate	„	Released from the dorsal position with difficulty									
Amylenhydrate	„	„		„	„	„	„	without	„		
Detonal	„	„		„	„	„	„	„	„		

When the injection of 0·00075 grm. of detonal per 1 grm. frog was executed the values shown in Table VI were obtained:

TABLE VI.

Narcotic.	Interval between injection and sleep.		Interval between injection and stoppage of respiration.		Duration of sleep.		Duration of the cessation of respiration.		Interval between awaking and recovery.	
	Hr.	Min.	Hr.	Min.	Hr.	Min.	Hr.	Min.	Hr.	Min.
Detonal	0	9	0	9	2	10	1	21	0	43

(3) The experiments were still further continued with the higher homologous acylurethanes and some allied compounds together with urethane, detonal and epronal in the manner described in the previous experiments, but in the case of the substances which do not dissolve in water in such a degree as to cause the narcotic action, they were injected in the state of emulsion with 4% gum arabic.

The present experiments were performed in December 1915, while the pervious ones in June the same year. The results of experiments will be given in the following table:

TABLE VII.

Narcotics.	Minimum doses per 1 grm. frog in aq. solution,		Minimum doses per 1 grm. frog in emulsion,		Strengths of narcotic action.
	in grm.	in gram-mol.	in grm.	in gram-mol.	
Urethane	0·001700	1910×10^{-8}	—	—	10
Detonal	0·000400	214×10^{-8}	0·001040	5560×10^{-9}	90
Epronal	0·000225	112×10^{-8}	0·000400	1990×10^{-9}	170
Dipronal	0·000120	56×10^{-8}	—	—	340
Probnal	0·000090	39×10^{-8}	0·000150	655×10^{-9}	500
Dibnal	—	—	0·000160	656×10^{-9}	500
Oenanthylylurethane	—	—	0·000600	2985×10^{-9}	90–170
N-Isoamylurethane	0·000320	200×10^{-8}	—	—	95
Adaline	0·000080	34×10^{-8}	—	—	560
α-Bromethyl-propylaceturea	0·000060	24×10^{-8}	—	—	800

In this case the strengths of the narcotic action of the different substances with the exception of dibnal and oenanthylylurethane, as

given in the table, have been deduced by dividing the minimum dose of urethane in aqueous solution by that of each narcotic in the same and then multiplying the quotient by 10 so as to take that of urethane as 10 × unit. The minimum doses of dibnal and oenanthylylurethane, however, on account of their feeble solubilities in water, have been determined in the state of emulsion, and also those of detonal and epronal in the same for comparison. Since the minimum doses of probnal and dibnal are almost equal in the state of emulsion, the strength of the narcotic action of dibnal may be assumed as almost equal to that of probnal, consequently as 500. That of oenanthylylurethane in emulsion lying between the values of detonal and epronal, the strength of its narcotic action ought to lie between 90 and 170.

IV. The Failure of the Heart.

The experiments were conducted in June 1915, according to the usual method by using the extirpated hearts of Rana esculenta. The narcotics were dissolved in Ringer's solution, and the rates of action upon the heart compared in the concentrations of 0·15, 0·12 and 0·09% solutions of each substance, noticing the duration of the heart-beat in minutes and seconds until its stoppage took place after the charge of the narcotics.

Solution in 0·15%.

Table VIII.

Narcotics.	Number of experiments.	Durations of the heart-beat.	
		Min.	Sec.
Epronal	I	2	0
	II	1	0
Hedonal	I	0	50
	II	0	20

Narcotics.	Number of experiments.	Durations of the heart-beat.	
		Min.	Sec.
Trional	I II III	More than 30 „ „ „ „ „ „	Heart-beat in normal condition.
Bromural	I II III	12 5 6	0 0 0
Amylenhydrate	I II	More than 30 „ „ „	0 0
Chloralhydrate	I II III	13 27 —	0 0 —
Veronal	I II III IV	20 23 30 32	
Detonal	I II III	More than 30 „ „ „ „ „ „	Heart-beat in normal condition.

Solution in 0·12%.

TABLE IX.

Narcotic.	Number of experiments.	Durations of the heart-beat.	
		Min.	Sec.
Hedonal	I II	0 7	40 0

Narcotic.	Number of experiments.	Durations of the heart-beat.	
		Min.	Sec.
Epronal	I	More than 30	
	II	4	0
	III	5	0
	IV	4	0
	V	7	0

Solution in 0·09%.

TABLE X.

Narcotics.	Number of experiments.	Durations of the heart-beat.	
		Min.	Sec.
Epronal	I	25	0
	II	More than 30	0
	III	„ „ „	0
	IV	„ „ „	0
	V	„ „ „	0
	VI	„ „ „	0
Hedonal	I	More than 30	0
	II	„ „ „	0
	III	22	0
Bromural	I	More than 30	0
	II	„ „ „	0
	III	25	0

The results of the experiment performed in December 1915, with the higher homologous acylurethanes and some allied compounds together with urethane, detonal and epronal will be given in the following table :

TABLE XI.

Narcotics.	Number of experiments.	Concentration in grm.-mol. in 1 liter Ringer's solution.	Durations of the heart-beat.	
			Min.	Sec.
Urethane	I	0·2240	2	10
	II	„	1	30
	III	„	2	0
	IV	0·2020	5	25
	V	„	7	15
	VI	„	6	11
Detonal		0·0270	Five experiments were carried out. In each the heart-beat continued more than 30 minutes although weak.	
Epronal	I	0·00746	2	40
	II	„	3	15
	III	„	0	30
	IV	0·00447	4	0
	V	„	7	20
	VI	„	6	50
Dipronal		0·00180	Four experiments were carried out. In each the heart-beat continued more than 30 minutes although weak.	
Probnal	I	0·00130	4	40
	II	„	4	33
	III	„	7	11
	IV	,	6	45
Dibnal		0·00020	Three experiments were carried out. In each no noticeable change was observed.	
Oenanthylyl-urethane		0·00045	Three experiments were carried out. In each no noticeable change was observed.	
N-Isoamyl-urethane	I	0·00470	5	20
	II	„	4	31
	III	„	7	12
	IV	0·00315	22	11
	V	„	24	34
	IV	„	11	20

Narcotics.	Number of experiments.	Concentration in grm.-mol. in 1 liter Ringer's solution.	Durations of the heart-beat.	
			Min.	Sec.
Adaline	I	0·00086	Three experiments were carried out. In each no noticeable change was observed.	
α-bromethyl-propylaceturea	I	0·00081	Three experiments were carried out. In each no noticeable change was observed.	

V. The Maximum and Lethal Doses of Epronal for the Rabbit.

(1) Epronal, 0·3 grm. per 1 kilog. rabbit was charged to the stomach in the form of 3% emulsion.

1'° 20$^{min.}$ P.M. Dosed; respiration counted 92.
1'° 40$^{min.}$ P.M. Shut the eyes in the sedative condition, but moved to and fro.
2'° 50$^{min.}$ P.M. Shut the eyes, but walked by persuation.
3'° 50$^{min.}$ P.M. As it was, but in a somewhat healthy condition.

(2) Epronal, 0·5 grm. per 1 kilog. rabbit.

1'° 25$^{min.}$ P.M. Dosed; respiration counted 70.
1'° 45$^{min.}$ P.M. Fell into a deep sleep; respiration counted 55.
2'° 35$^{min.}$ P.M. Scented around, but the paralyzed hind legs did not allow to walk; continued the sleep further.
3'° 35$^{min.}$ P.M. Shut the eyes, but walked by persuation; respiration counted 60.
4'° 0$^{min.}$ P.M. In healthy condition.

(3) Epronal, 1·0 grm. per 1 kilog. rabbit.

1'° 30$^{min.}$ P.M. Dosed; respiration counted 71.
1'° 40$^{min.}$ P.M. Shut the eyes, but walked to and fro.
1'° 50$^{min.}$ P.M. Fell into a sleep; respiration counted 60.
2'° 15$^{min.}$ P.M. Moved; but continued the sleep.
2'° 30$^{min.}$ P.M. The paralyzed hind legs did not allow to get up and fell into the sleep again; respiration counted 55.

2'° 53$^{min.}$ P.M.	The rattling sound in trachea and the wriggle of intestine were noticed.
4'° 20$^{min.}$ P.M.	Continued the sleep; respiration counted 55.
5'° 20$^{min.}$ P.M.	Could not get up by the paralysis of hind legs but became sensible; respiration counted 55.
The next day.	Recovered.

(4) Epronal, 1·5 grm. per 1 kilog. rabbit.

11'° 5$^{min.}$ A.M.	Dosed; respiration counted 80.
11'° 15$^{min.}$ A.M.	Fell into a deep sleep.
11'° 50$^{min.}$ A.M.	The hind legs paralyzed; respiration counted 60.
1'° 40$^{min.}$ P.M.	Continued the sleep; respiration counted 60.
3'° 30$^{min.}$ P.M.	As it was.
4'° 40$^{min.}$ P.M.	Continued the sleep; the wriggle of intestine was noticed.
5'° 0$^{min.}$ P.M.	Respiration counted 48.
6'° 0$^{min.}$ P.M.	Continued the sleep; respiration counted 55.
The next day.	Recovered.

(5) Epronal, 2·0 grm. per 1 kilog. rabbit.

11'° 10$^{min.}$ A.M.	Dosed; respiration counted 70.
11'° 17$^{min.}$ A.M.	Fell into a deep sleep; respiration counted 57.
11'° 40$^{min.}$ A.M.	The hind leges paralyzed; respiration counted 50.
12'° 15$^{min.}$ P.M.	Continued the sleep; respiration counted 47.
3'° 30$^{min.}$ P.M.	Endeavoured to get up but in vain; respiration counted 32.
4'° 0$^{min.}$ P.M.	The wriggle of intestine was observed.
5'° 0$^{min.}$ P.M.	Continued the sleep; respiration counted 33.
6'° 0$^{min.}$ P.M.	As it was.
The next day.	Recovered.

(6) Epronal, 2·5 grm. per 1 kilog. rabbit.

10'° 0$^{min.}$ A.M.	Dosed; respiration counted 90.
10'° 20$^{min.}$ A.M.	Fell into a sleep; respiration counted 60.
12'° 0$^{min.}$ A.M.	The wriggle of intestine was observed; respiration counted 50.

5'° 0$^{min.}$ A.M.	Continued the deep sleep; respiration counted 40.
The next day.	Continued the sleep all the day; respiration counted 35–40.
At noon the day after next.	Became sensible and took some food.
4'° 0$^{min.}$ P.M.	Moved to and fro with paralyzed hind legs.
The next day succeeding.	Died.

(7) Epronal, 3·0 grm. per 1 kilog. rabbit.

3'° 0$^{min.}$ P.M.	Dosed; respiration counted 80.
3'° 20$^{min.}$ P.M.	Fell into a sleep.
4'° 0$^{min.}$ P.M.	Continued the sleep; respiration counted 60.
6'° 0$^{min.}$ P.M.	Continued the sleep; respiration counted 50.
At noon the day after next.	Died.

VI. The Influence of Epronal upon the Blood-pressure, Vagus and Respiratory Centre.

In about an hour after dosing 1·5 grm. epronal per 1 kilog. rabbit, a rabbit fell into a sleep. The blood-pressure, then observed, was found to be almost constantly 100 mm. in the mercury column as is usually noticed in the normal rabbit; by giving stimulation to the vagus or an obstruction to respiration the degradation of the blood-pressure took place as shown in the curve given at the end of this article. Such facts show that the vagus and the respiratory centre would not be influenced at all.

In conclusion, I beg to offer my best thanks to Professors Kuhara and Morishima for their valuable suggestions and guidance in carrying out this research.

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